of tumors as the elected species. Claim 1 has also been amended to insert "at the site, wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures." Support is found on page 17, lines 16-17; page 18, lines 3-11.

Claim 6 has been amended to recite that the enzyme is administered when the individual has cancer as evidenced by palpable tumors. Support is found at page 19, lines 22-27.

Support for new claim 19, which recites the dosage range for the use of chondroitinase AC to inhibit angiogenesis in tumors, is found at page 12, lines 18-20.

Support for new claim 20 is found at page 8, lines 8-11 and page 9, lines 26-29.

Support for new claim 21 is found at page 12, lines 9-11.

Support for new claims 22 and 23 is found on page 12, lines 4-6.

Support for new claims 24 and 25 is found on page 18, lines 12-24.

Rejections under 35 U.S.C. 102

Claims 1-9 were rejected under 35 U.S.C. 102(b) as disclosed by Takeuchi, Br. J. Cancer 26, 115 (1972). This rejection is respectfully traversed.

Takeuchi administers enzyme **prior to or with** tumor cells injected into mice and shows that the tumor cells do not grow as well. Takeuchi does not demonstrate that one can inject enzyme into established tumors and inhibit further growth, nor inhibit angiogenesis – which requires endothelial cells. All of Takeuchi's studies were done solely on and assessing tumor cells.

The examiner's statement that the mechanism is the same since the method steps are the same is not correct. Takeuchi does not inhibit angiogenesis but some other mechanism which prevents the injected cells from forming tumors. The data at col. 1 of page 118 and the discussion at col. 1, of page 119, indicates that the proposed mechanism has nothing to do with angiogenesis. Indeed, the examiner is directed to the second paragraph of the summary on page 1, stating that chondroitin sulphate promotes tumor growth. One skilled in the art would reasonably infer from this that it is the cleavage of chondroitin sulfate at the site of injection that limits tumor growth.

A rejection under 35 U.S.C. 102 requires the disclosure in a single reference of each claimed limitation. Takeuchi does not disclose all claimed limitations in each of claims 1-9.

There is no teaching that chondroitinase inhibits angiogenesis. Claim 1 is specific to inhibition of angiogenesis.

Claim 3 is specific to a mammalian enzyme. Takeuchi does not disclose a mammalian enzyme.

Claims 6 and 7 recite administering enzyme when there are already palpable tumors. Claim 19 further recites a specific dosage of chondroitinase AC. Claim 21 requires administration of the enzyme after excision of the tumor. Takeuchi discloses administration only with cells to see if they formed tumors.

None of the angiogenesis related disorders of claim 8 are disclosed by Takeuchi.

Claims 9, 22 and 23 require systemic administration. Takeuchi discloses only local administration by subcutaneous injection.

Claim 11 requires administration by a controlled or sustained release formulation, neither of which is disclosed by Takeuchi.

Claim 20 requires the co-administration of another drug. Takeuchi makes no mention of another drug.

Claims 24 and 25 define administration of chondroitinase B. Takeuchi makes no mention of chondroitinase B.

In summary, Takeuchi does not disclose the subject matter of any of claims 1-11 and 19-25.

Rejection under 35 U.S.C. 103

Claims 1-11 were rejected under 35 U.S.C. 103 as obvious over Takeuchi in combination with JP 51075042. Claims 1-11 were also rejected under 103 as obvious over Takeuchi in combination with JP 51075042 and U.S. Patent No. 4,696,816 to Brown. These rejections are respectfully traversed.

The Japanese application

The Japanese application does not appear to be in the slightest way relevant. The application refers to compounds produced by reacting guanido fatty acid amides with sulphanylamide to treat tumors. This has nothing to do with anything that is claimed other than

the fact that studies were performed with the same tumor cell lines as the examples. Applicants agree that the cell line used by Takeuchi will form tumors in mice.

Brown

Brown teaches the use of chondroitinase, as well as collagenase, to break down cartilaginous tissue. See col. 4, lines25-27 and 42-45. There is no teaching of using chondroitinase or any other glycosaminoglycan degrading enzyme to prevent angiogenesis, which is not cartilaginous tissue but has to do with the migration and proliferation of endothelial cells.

Brown fails to make up for the deficiencies in Takeuchi, alone or in combination with the JPA. If one combined the references, one would be led to use chondroitinase AC to remove cartilage or polysaccharide in tumor cells, but only if administered before or with the tumor cells.

There is no motivation to combine the elements defined by applicants' claims, much less to treat the disorders as defined by claim 8, or in treating tumors as defined by claims 6, 7, and 21. There is no teaching in any of the references to administer enzyme systemically, or in controlled or sustained release forms. There is no teaching to use chondroitin B. There is no teaching of any combination therapy.

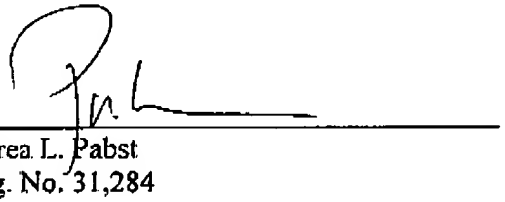
Even if motivation to combine, and the elements missing from the cited art, were suddenly to appear, there is nothing that would lead one to any expectation of success.

The test for obviousness is whether the prior art discloses the claimed elements, and provides the motivation to combine as applicants have done, with a reasonable expectation of

success. In the field of cancer, there is no expectation of success based on studies in which tumors are treated *ex vivo*, or at the same time as they are injected into an animal. The literature is replete with failures based on such data. This data is simply not predictive of success in treating established tumors. Therefore the cited references do not make obvious claims 1-11 and 19-25.

Allowance of claims 1-11, as amended, and new claims 19-25, is therefore earnestly solicited.

Respectfully submitted,



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APPENDIX: Claims marked as Amended

1. (twice amended) A method to decrease [tumor growth] angiogenesis comprising administering to [tumors in] a site in an individual in need of treatment thereof an effective amount of a purified glycosaminoglycan degrading enzyme to decrease angiogenesis [and thereby reduce tumor growth] at the site, wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures.

2. The method of claim 1 wherein the enzyme is selected from the group consisting of bacterial glycosaminoglycan degrading enzyme is selected from the group consisting of heparinase 1 from *Flavobacterium heparinum*, heparinase 2 from *Flavobacterium heparinum*, heparinase 3 from *Flavobacterium heparinum*, chondroitinase AC from *Flavobacterium heparinum*, and chondroitinase B from *Flavobacterium heparinum*, heparinase from *Bacteroides* strains, heparinase from *Flavobacterium* Hp206, heparinase from *Cytophagia* species, chrondoitin sulfate degrading enzymes from *Bacteroides* species, chrondoitin sulfate degrading enzymes from *Proteus vulgaris*, chrondoitin sulfate degrading enzymes from *Micrococcus*, chrondoitin sulfate degrading enzymes from *Vibrio* species, chrondoitin sulfate degrading enzymes from *Arthrobacter aurescens*, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.

3. The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. The method of claim 1 wherein the enzyme is a chrondroitinase.

5. The method of claim 4 wherein the chondroitinase is chondroitinase AC.

6. (amended) The method of claim 1 wherein at the time the enzyme is administered the individual has cancer as evidenced by palpable tumors.

7. The method of claim 6 wherein the cancer is a solid tumor and the enzyme is chondroitinase AC.

8. The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of rheumatoid arthritis; psoriasis; ocular angiogenic diseases, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; disease of excessive or abnormal stimulation of endothelial cells, Crohn's disease, atherosclerosis, scleroderma, and hypertrophic scars, diseases that have angiogenesis as a pathologic consequence, adhesions, scarring following transplantation, cirrhosis of the liver, pulmonary fibrosis following acute respiratory distress syndrom or other pulmonary fibrosis of the newborn, endometriosis, polyposis, obesity, uterine fibroids, prostatic hypertrophy, and amyloidosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. The method of claim 1 wherein the enzyme is administered topically or locally at or adjacent a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

19. The method of claim 7 wherein the dosage is in the range of 0.1 to 250 IU chondroitinase AC/tumor for tumors in the size range from 20 mm^3 to 15 cm^3.

20. The method of claim 1 wherein the enzyme is administered in combination with another active agent selected from the group consisting of antibiotics, cytokines, cytotoxic agents, and anti-inflammatories.

21. The method of claim 7 wherein the enzyme is administered after excision of the tumor.

22. The method of claim 9 wherein the enzyme is administered by a route selected from the group consisting of intravenous, intra-cranial, and depo.

23. The method of claim 9 wherein the enzyme is administered using an infusion pump.

24. The method of claim 1 wherein the enzyme is chondroitinase B.

25. The method of claim 8 wherein the enzyme is chondroitinase B.

APPENDIX: Clean Copy of Claims as Amended

1. (twice amended) A method to decrease angiogenesis comprising administering to a site in an individual in need of treatment thereof an effective amount of a purified glycosaminoglycan degrading enzyme to decrease angiogenesis at the site, wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures.

2. The method of claim 1 wherein the enzyme is selected from the group consisting of bacterial glycosaminoglycan degrading enzyme is selected from the group consisting of heparinase 1 from *Flavobacterium heparinum*, heparinase 2 from *Flavobacterium heparinum*, heparinase 3 from *Flavobacterium heparinum*, chondroitinase AC from *Flavobacterium heparinum*, and chondroitinase B from *Flavobacterium heparinum*, heparinase from *Bacteroides* strains, heparinase from *Flavobacterium* Hp206, heparinase from *Cytophagia* species, chrondoitin sulfate degrading enzymes from *Bacteroides* species, chrondoitin sulfate degrading enzymes from *Proteus vulgaris*, chrondoitin sulfate degrading enzymes from *Microcossus*, chrondoitin sulfate degrading enzymes from *Vibrio* species, chrondoitin sulfate degrading enzymes from *Arthrobacter aurescens*, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.

3. The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. The method of claim 1 wherein the enzyme is a chrondroitinase.

5. The method of claim 4 wherein the chondroitinase is chondroitinase AC.

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6. (amended) The method of claim 1 wherein at the time the enzyme is administered the individual has cancer as evidenced by palpable tumors.

7. The method of claim 6 wherein the cancer is a solid tumor and the enzyme is chondroitinase AC.

8. The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of rheumatoid arthritis; psoriasis; ocular angiogenic diseases, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; disease of excessive or abnormal stimulation of endothelial cells, Crohn's disease, atherosclerosis, scleroderma, and hypertrophic scars, diseases that have angiogenesis as a pathologic consequence, adhesions, scarring following transplantation, cirrhosis of the liver, pulmonary fibrosis following acute respiratory distress syndrom or other pulmonary fibrosis of the newborn, endometriosis, polyposis, obesity, uterine fibroids, prostatic hypertrophy, and amyloidosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. The method of claim 1 wherein the enzyme is administered topically or locally at or adjacent a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

19. The method of claim 7 wherein the dosage is in the range of 0.1 to 250 IU chondroitinase AC/tumor for tumors in the size range from 20 mm^3 to 15 cm^3.

20. The method of claim 1 wherein the enzyme is administered in combination with another active agent selected from the group consisting of antibiotics, cytokines, cytotoxic agents, and anti-inflammatories.

21. The method of claim 7 wherein the enzyme is administered after excision of the tumor.

22. The method of claim 9 wherein the enzyme is administered by a route selected from the group consisting of intravenous, intra-cranial, and depo.

23. The method of claim 9 wherein the enzyme is administered using an infusion pump.

24. The method of claim 1 wherein the enzyme is chondroitinase B.

25. The method of claim 8 wherein the enzyme is chondroitinase B.